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23-11-2022

Bachelor of Pharmacy V Semester End Semester Examination

November - 2022

3662

INDUSTRIAL PHARMACY - I

Instructions to the candidates:

1. Do not write anything on question paper except Roll Number, otherwise it shall be deemed as an act of indulging in unfair means and action shall be taken as per rules.
2. Section-A contains Q-1 and Q-2 with Five (5) questions each. All the Ten very short type questions are compulsory and carry equal marks (10 x 2 = 20).
3. Section-B contains Q-3, Q-4 and Q-5. Answer any TWO questions among the three descriptive type questions and carry 10 marks each. (2 x 10=20).
4. Section-C contains Q-6 and Q-7 with FIVE (5) and FOUR (4) sub divisions. Answer any FOUR (4) and THREE (3) questions of choice among the short answer type questions and all carry 5 marks each. (7 x 5 = 35)

Duration: 3 Hours | No. of Pages in this Question Paper: 1 | Total Marks: 75

Section – A

1. Answer the following questions in very short (Maximum 20 words): 5 x 2 = 10
   a) What are disintegrants and give two examples?
   b) What is LAL test?
   c) Write advantages of ophthalmics.
   d) What is meant by preformulation studies?
   e) Define bloom strength.
2. Answer the following questions in very short (Maximum 20 words): 5 x 2 = 10
   a) List out manufacturing defects in tablets.
   b) List evaluation of aerosols.
   c) What are ideal properties of shampoos?
   d) What is intrinsic solubility of drugs?
   e) Name the methods of adjustment of isotonicity.

Section – B

Answer (any Two) of following questions in Long answer: 2 x 10 = 20

3. Define tablet. List types of tablets. Explain in detail evaluation parameters of tablet.
4. Explain in detail cold filling & pressure filling methods of aerosols.
5. Define capsule. Differentiate between hard & soft gelatin capsules. Elaborate on manufacturing of soft gelatin capsules.

Section – C

6. Answer (Any Four) of the following in short answer: 4 x 5 = 20
   a) Explain chilsonator with diagram.
   b) Write specifications & method of preparation WFI.
   c) Methods of enhancing solubility of drugs.
   d) Classify liquid orals. State its ideal characteristics.
   e) A note on propellants.
7. Answer (Any Three) of the following questions in short answer: 3 x 5 = 15
   a) Formulation of lipstick.
   b) Sugar coating of tablets.
   c) Quality control tests for packaging material.
   d) Lyophilization.

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Unit - 1st - Preformulation studies :- 01/07/2022

* It can be defined as an "investigation of physical & chemical properties of a drug substance with excipients"

* The phase of "research & development" of a drug molecule in order to "develop safe, effective & stable dosage form".

Goals - To establish the physico-chemical parameters of new drug substance.-
- To establish the physical characteristics -
- To establish the kinetics rate profile.-
- To establish the compatibility with the common excipients

Objectives -
- To develop the stable, safe & effective dosage forms -
- It is important to have an understanding of the physical detail (report) of a drug substance before dosage form development.-
- It is the 1st step in reasonable (logical) development of a dosage form of a drug substance -
- It generates useful information to the optimum drug delivery system.-

- Terms - IND ⇒ Investigation new drugs -
NDA ⇒ New drugs approval -
ANDA ⇒ Abbreviated new drugs application -

05/07/2022

Study of physico-chemical characterisitics of drug substance

[Principle area of preformulation research]

a) Organoleptic characters -]
b) Bulk characters -] ⇒ physical properties -
c) Solubility analysis -
d) Stability analysis -] ⇒ Chemical properties -

a) Organoleptic characters -

· Colour, odour & taste of the new drug must be recorded -

· Colour	· Odour	· Taste
· Off-white	· Fruity	· Acidic
· Cream yellow	· Aromatic	· Bitter
· Tan	· Odourless	· Sweet
· Shiny	· Pungent	· Tasteless

b) Bulk characters -

i) Crystallinity & polymorphism -
ii) Hygroscopicity -
iii) Fine particle characterization -
iv) Powder flow properties -

07/07/2022

i) Crystallinity - Crystal nature & internal structure of drug can affect bulk & physi-co-chemical property of molecule. -

* Crystal nature - is description of outer appearance of crystal
* Internal structure - is molecular arrangement within the solid. -
* Change with internal structure usually alters crystal nature. -

* Different shapes of crystals - Cubic, tetragonal, triclinic, orthombic, hexagonal, monoclinic & trigonal -

* Internal structure compounds is classified as -
  · Crystalline - ⇒ 3-dimensional array -
  · Amorphous - ⇒ Randomly placed -

** Solubility & dissolution rate are greater for amorphous form than crystalline. -

* Amorphous form has higher thermodynamic energy. -

* Polymorphism -
  · It is the ability of the compound to crystallize as more than one separate crystalline species with different internal lattice.

* Different crystalline forms are called polymorphs. -

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* Polymorphs are two types -
- Enatio-tropic - Change one form into another form
- Mono-tropic - ⇓ by varying temp. or pressure -
  ⇓ eg. Sulphur -
- One polymorph which is unstable at all temp. & pressure
  eg. - Glyceryl stearate -

* Polymorphism effect - Solubility -
  - Melting point -
  - Density -
  - Hardness -
  - Compression characteristic -

eg. Chloram-phenicol exist in A, B & C forms -
B-form is more stable & most preferable -

* Analytical methods for the characterization of solid forms -
- Microscopy -
- Hot stage microscopy -
- X-ray diffraction -
- IR (infra-red) spectroscopy -
- Proton magnetic resonance (PMR) -
- Nuclear magnetic resonance (NMR) -
- Scanning electron microscopy (SEM) -

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iii. Hygroscopicity - many drug substances have a tendency to adsorb atmosphere moisture -

* The degree of Hygroscopicity is classified into 4-classes -
- Slightly hygroscopic ⇒ ≥ 0.2% w/w & < 2% w/w -
- Hygroscopic ⇒ ≥ 2% w/w & < 15% w/w -
- Very hygroscopic ⇒ ≥ 15% w/w -
- Deli-quescent ⇒ form a solution*

* Analytical method for hygroscopicity -
- Gravimetry -
- Karl Fischer titration -
- Gas chromatography -

iii. Fine particles characterization -
- Particle size is characterized using these terms -
- Very coarse -
- Coarse -
- Moderately coarse -
- Fine -
- Very fine -

* Particle size can influence variety of important factors -
- Dissolution rate -
- Suspendability -
- Uniform distribution -
- Penetrability -
- Lack of grittiness -

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* Analytical method for particle size-

- Sieving shaker method - (5μ to 150μ)
- Microscopy method (0.2μ to 100μ) -
- Sedimentation rate method (1μ to 200μ) -
- Light energy diffraction (0.5μ to 500μ) -
- Laser holography (1.4μ to 100μ) -

iv) Powder flow properties - The flow properties depends upon -
- force of friction -
- Cohesion b/w one particle to another -

* Powder flow properties can be affected by change in - particle size -
- shape & density -

* Powder flow properties can be determine by -
- "Angle of repose" ($\tan\theta = h/r$)

* Analytical method for angle of repose -

- Static angle of repose - fixed-funnel method -
  - fixed-cone method -
- kinetic/dynamic method - Rotating cylinder method
  - Tilting-box method -

** Measurement of "free flowing powder" by -
- Compressibility (Carr's index) -

{VES-S-SUP}

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c) Solubility analysis -
- i) Ionization Constant - Pka
- ii) pH solubility profile -
- iii) Common ion effect - ksp -
- iv) Thermal effects -
- v) Solubilization -
- vi) Partition co-efficient -
- vii) Dissolution -

* Solution phase equilibrium with solid phase at a stated temperature & pressure -

* Descriptive term	Parts of solvent required for 1-part of solute
Very soluble	Less than 1 -
Freely soluble	From 1 to 10 -
Soluble	From 10 to 30 -
Sparing soluble	From 30 to 100 -
Slightly soluble	From 100 to 1000 -
Very slightly soluble	From 1000 to 10,000 -
Practically insoluble	10,000 & over -

i) Ionization Constant [Pka] OR Dissociation Constant - of drug -

* Degree of Ionization depends on pH -

* Determined by - Uv-spectroscopy - Titrimetric method
  - Potentiometric titration -

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* Henderson-Hasselbalch equation -
  - For acidic compd.- $pH = pka + \frac{[\text{Un-Ionized drug}]}{[\text{Ionized drug}]}$
  - For basic compd.- $pH = pka + \frac{[\text{Ionized drug}]}{[\text{Unionized drug}]}$

iii) Solubilization -
It is the process by which apparent solubility of an otherwise sparingly soluble subs is increased by the presence of surfactant.

* General method of increase the solubility -
  - Addition of co-solvent.
  - pH change method.
  - Reduction of particle size.
  - Temperature change method.
  - Addition of surfactant.
  - Dielectrical constant.
  - Complexation.

iii) Partition co-efficient -
- Measurement of the drug nature - ⇓

$\left\{ P = \frac{\text{Corganic}}{\text{Caqueous}} \right\}$ - The ability to cross the cell membrane.

iii) Dissolution - It is a process by which molecules of a solute are dissolved in a solvent vehicle.

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d) Stability analysis -
  i) Solution stability -
  ii) Solid state stability -
  iii) Drug-excipient compatibility -

i) Solution stability -
- The decomposition of drug occurs through -
  - Hydrolysis - (dissociation)
  - Oxidation -
  - Reduction -
  - Racemisation -
  - Polymerization -

ii) Solid state stability - Depend on the temperature, light, humidity, polymorphic change & oxidation. -

iii) Drug-excipient compatibility -
It is play a very important role in the preformulation studies of oral dosage forms. -

- Oxidation - It is very common pathway for drug degradation in both liquid & solid formulation.
  - The gain of O_2, loss of hydrogen-electron.
- Reduction - The gain of hydrogen, loss of O_2.
- Hydrolysis - It is the cleavage of chemical bonds by the addition of water.

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- Racemization – It the process in which one enantiomer of a compound converst to the other enantiomer.-

* Racemization is optically inactive
  L-form ⇌ D-form

** If the racemization - The enantiomers are present in equal quantities
  ⇓
  racemic / racemate -

- Polymerization –
  It is process in which reacting monomer molecules together in a chemical rxn to form polymer chain.-

* It is a continuous reaction b/w molecules -
* More than one monomer reacts to form a polymer

BCS classification of drugs & its significant -

* The Bio-pharmaceutical classification system is a scientific frame work for classifying a drug substance
  ⇓ Based on

- It's "aqueous solubility, intestinal permeability & dissolution rate".-

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* BCS was 1st developed in 1955 by Amidon etal -

* Bio-pharmaceutical classification system for drug -
  ⇓ on based of solubility & permeability -

Class	Solubility	Permeability	Example
Class-I	High	High	-Metaprolol, Propranolol-
Class-II	Low	High	-Naproxen, Nifedipine-
Class-III	High	Low	-Cimitidine, metformin-
Class-IV	Low	Low	-Taxol, Clorthiazole-

* Factor affecting on BCS -
  - Solubility -
  - Permeability -
  - Dissolution -

- Solubility – It is the ability of drug dissolved in a given solvent under standard conditions of temperature, pressure & pH. -
- Permeability - The drug to pass the biological membr
- Dissolution – It is process in which solid substance transfer to liquid phase.-

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* Application of BCS -
  - To predict invivo performance of drug product using solubility & permeability measurement. -
- To use in biowaiver considerations -
- For research scientist to decide upon which drug delivery technology to follow & develop. -
- The regulation of bio-equivalence of the drug product during scale up & post approval -
- Help in earliest stages of drug discovery research

Application of preformulation considerations in the development of -

(A) Solid dosage forms -
  - Solid dosage forms are the most widely marketed & administered drugs presently (nowadays). -

* Almost 70% of the administered drugs are in solid states. - due to its high safety & low cost. -

- following parameters are to be studied -
  i) Organoleptic properties - (Colour, odour, taste) -
  ii) Purity -
  iii) Particle size, shape & surface area -
  iv) Dissolution & solubility -
  v) Partition coefficient, & Ionization Constant -
  vi) Permeability across the membrane -

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  vii) Crystal properties & polymorphism -
  viii) Density, flowability & wettability etc -
  ix) Stability studies -

(B) Parenteral/Liquid dosage forms -
  - It is a injectable route of administration. -

* Parenteral is derived from greek word -
  - Para = outside -
  - Enter on = intestine -

- Studies of parenteral dosage form include -
  a) Bulk characterization - i) Particle size -
     ii) Powder flow property -
     iii) Crystallinity & polymorphism
  b) Solubility study - i) pKa determination -
     ii) Common ion effect -
     iii) Partition coefficient -
  c) Stability study - i) Solution stability -
     ii) Solid state stability -
  d) Spectroscopy - i) UV - spectrophotometry -
     ii) IR - spectrophotometry -
     iii) X-ray diffraction method -
  e) Microscopy -
     - In this technique substance are examined under micro-scope - (shape, thickness, size etc).

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f) Chromatography - i) Thin layer chromatography
ii) Gas chromatography
iii) High pressure liquid chromatography (HPLC)
⇓
Obtain analytical data-

G D MEMORIAL COLLEGE OF PHARMACY, JODHPUR

FIRST THEORY SESSIONAL EXAMINATION- Sept 2022

Class: B. Pharm. 03 YEAR/ V Sem (2021-22) **Roll No.: 18**
Subject: Industrial Pharmacy I **Max. Marks: 30**
Subject Code: BP 502T **Time: 1 Hour**
Day & Date of Exam: 20/09/2022

Note : Support your answers with relevant example

A . OBJECTIVE TYPE QUESTIONS. (ANSWER ALL QUESTIONS). (5x2=10 Marks)

1. Define Preformulation Studies.
2. Write advantages and disadvantages of Tablets.
3. Write name of Defects in Tablets.
4. Define Elixirs.
5. Write name of evaluation test for emulsion.

B. SHORT ANSWER TYPE (ANSWER ANY TWO QUESTIONS) (02 x 05=10 Marks)

1. Classify Tablets. Explain defects in tablets with suitable remedies

Unit-2nd # Tablets & Liquids Oral # 03/08/022

Tablets

- Tablet is a solid unit dosage form.-
- The solid unit dosage form of medicaments/medicamats with suitable excipients.-
- Tablets are prepared by the 'Compression method' are called compressed tablets.-

- Tablets => Circular in shape -
  => Biconvex/flat in shape-

- Advantages -
  - Easy to be administered.-
- Easy to be dispensed.-
- More stable dosage form.-
- Maintain the accuracy of dosage.-
- Economical dosage form.-
- Bitter & nauseous substances can be given easily in tablet form after suitable coating.-
- The most compact of all dosage forms.-
- Easiest & cheapest as packing & transport -
- Better favorable to a large scale production -

- Dis-advantages-
  - Drugs resist compression into tablet form due to amorphous nature/low density character-
- Slow/low dissolution properties are difficult to convert into tablets-
- Bitter tasting drugs may require a special type of coating which may increase the cost of finished tablets -

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Types of tablets - according to route of administration (function) -

1. Tablets ingested orally -
2. Tablets used in oral cavity -
3. Tablets administered by other routes -
4. Tablets used to prepare solution -

1. Tablets ingested orally -
   i) Compressed tablets - (Uncoated tab.) -
   ii) Multi-compressed tablets -
   iii) Multi-layered tablets -
   iv) Sustained action tablets -
   v) Enteric coated tablets -
   vi) Sugar coated tablets -
   vii) Film coated tablets -
   viii) Chewable tablets -

2. Tablets used in oral cavity -
   i) Buccal tablets -
   ii) Sub-lingual tablets -
   iii) Lozenge tablets & torches -
   iv) Dental cones -

3. Tablets administered by other routes -
   i) Implantation tablets -
   ii) Veginal tablets -

4. Tablets used to prepare solution -
   i) Effervencent tablets -
   ii) Dispensing tablets -
   iii) Hypodermic tablets -
   iv) Tablet triturates -

1) Tablets ingested orally -

· A majority of the tablets manufactured are ingested orally -

i) Compressed tablets (C.T.) -

· These tablets are uncoated & made by compression of granules. -

* These tablets are usually rapid dis-integration & drug release. -
* These tablets are contain water soluble drugs. -

ii) Multi-compressed tablets - (M.C.T.) -

· It is a special type of tablet making machine is used which provides two compressions. -

* These tablets are produce repeat action / prolonged action products -

iii) multi-layered tablets - / multi-coloured tablets -

· These tablets consist of two/more layers of materials compressed in the same tablets. -

* The colour of each layer may be the same or different. -

iv) Sustained action tablets -

· These tablets are used to get a sustained action of medicament.-

* These tablets are release the medicament in a sufficient quantity & maintain the maximum effective conc. of the drug in the blood.-
* These tablets are gaining popularity these days.-

v) Enteric Coated tablets - (Gastro-resistant tablets)-

· These are compressed tablets to bypass the stomach & get dis-integrated in the intestine only.-

* These tablets are made to release the drug in the highest conc. within the intestine.-
eg.- Anthelmentics & amoebicides.-

** Enteric coated tablets are prevent drugs release in stomach.-
** The enteric coat is insoluble at acidic pH of stomach but dissolve at alkaline pH of intestine.-
* Enteric coated material are polymeric subs-
eg.- cellulose acetate phthalate-
- cellulose acetate butyrate-
- Hydroxy-propy methyl cellulose - (HPME)-

vi) Sugar coated tablets -

· These are compressed tablets having a conc. sugar solution coating.

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vii) Film coated tablets -

· These are compressed tablets having a film coating of some polymer subs.-

* The film coating protects the medicament from atmospheric effects.-

· Film coated material are polymer subs-
eg.- Hydroxypropyl cellulose - (HPC)
- Hydroxy propyl methyl cellulose (HPMC)-
- Ethyl cellulose-

viii) Chewable tablets -

· These tablets are chewed in the mouth & broken into smaller pieces.-

* The disintegration time is reduced & the rate of absorption of the medicament is increased.-
eg.- Aluminium hydroxide tablets-
- Phenolphthalein tablets-

2.) Tablets used in oral cavity -

i) Buccal tablets -

· These tablets are placed in the buccal pouch | cheek.-
eg.- Ethisterone-

ii) Sublingual tablets -

· These tablets are placed under the tongue. - eg.- GTN (Glyceryl trinitrite) -

iii) Lozenge tablets & torches -

· These tablets are commonly used to treat coughing in common cold & sore throat. (wound/injury throat) -

iv) Dental cones -

· These are minor compressed tablet meant for placing them in the empty sockets after tooth extraction. -

* They prevent the multiplication of bacteria in the socket. -

3) Tablets administered by other routes -

i) Implantation tablets -

· These tablets are placed under the skin/inserted subcutaneously by minor surgical operation & are slowly absorbed. -

* Implants are mainly used for administration of hormones. - (eg. - Testosterone & deoxy-corticosteroneh

ii) Vaginal tablets -

· These tablets are meant to dissolve slowly in the vaginal cavity. -

* These tablets used to treat vaginal infections -

* Release - steroids, antibacterial agents, anti-septics/astringents -

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4.) Tablets used to prepare solutions -

i) Effervescent tablets -

· These tablets when added in water produce effervescence. -

· So. they dissolved rapidly in water due to the chemical reaction. -

* These tablets are protected from atmospheric moisture during storage. -

ii) Dispensing tablets -

· This type of tablets are added to a given volume of water to produce a solution. -

* These tablets are highly toxic, if taken orally by mistake. -

iii) Hypodermic tablets -

· These are compressed tablets which are composed of one/more drugs with water soluble ingredients. -

* These tablets are dissolved in sterile water/water for injection & administered by parenteral route. -

iv) Tablet triturates -

· These are small tablets usually cylindrical, compressed & contain a potent medicament with a diluent. -

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Manufacturing of tablets/ Compressed tablets - (Formulation of tablets)-

A) Preparation of granules for compression -
a) Weighing the ingredients -
b) Mixing the powdered ingredients & excipients -
c) Converting the mixed ingredients into granules -

B) Compression of granules into tablets -
C) Coating of tablets -
D) Quality control/evaluation of tablets -

Excipients / Excipients used in formulation of tablets -
→ It is an inert substance -

1) Diluents -
2) Granulating agents -
3) Binding agents -
4) Disintegrating agents -
5) Lubricants -
6) Adsorbents -
7) Organoleptic agents [Colouring agents, Flavouring agents & Sweetening agents]-

1) Diluents -
· The diluents is needed in the formulation of a tablet -
* ↑ bulk of tablets - (20t- 80%) -

eg- Lactose, sucrose, dextrose, starch, mannitol, sorbitol, sodium chloride, Dibasic Ca^{2+} phosphate dihydrate & Ca^{2+} sulphate dihydrate -

2) Granulating agents -
· Convert the fine powder into granules.-
eg- Water, alcohol, acetone, mucilage of starch, mucilage of acacia, mucilage of tragacanth, gelatin solution, iso-propyl alcohol -

3) Binding agents -
· Provides proper strength to the granules.-
eg- Gum acacia powder, gum tragacanth, gelatin, sucrose, methyl cellulose -

4) Disintegrating agents -
· Ensure disintegrating of the tablets into smaller particles -
* Disintegrating agents act in 3 ways -
i) By swelling -
ii) By producing effervescense -
iii) Melt at body temperature -
eg- Potato starch, maize starch, wheat starch, methyl cellulose, bentonite, sodium bicarbonate, Citric acid, tartaric acid & Coca butter -

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5) Lubricants -
· Improve the flow properties of granules & appearance of tablets -
* Lubricants are divided into 3 group -
i) Lubricants ⇒ Reduce interparticular friction -
ii) Glidants ⇒ Improve the flow properties of the granules
iii) Anti-adhesive agents ⇒ Prevent the sticking of tablet surface -
eg. - Talc, magnesium stearate, calcium stearate, sodium chloride, starch, boric acid, liquid paraffin & stearate acid. -

6) Adsorbing agents -
· Adsorb volatile oil, liquid extract & tincture -
eg. - starch, kaolin & magnesium carbonate -

7) Organoleptic agents -

a) Colouring agents -
· Improve the elegance/beauty of the tablets. -
eg. - Titanium oxide, Red ferric oxide, lead oxide, Copper sulfate & carbon black -, amaranth

Sweetening
b) Flavouring agents -
· Improve the taste of tablets -
eg. - Sucrose, lactose & mannitol -, aspartate

** Artificial sweetening agents like "Saccharin & Cyclamates" are not used nowadays

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c) Flavouring agents -
· More pleasant taste / sweet taste
eg. - Orange, lemon, Cinnamon, liquorice, ginger, raspberry & anise -

(B)# Granulation method | Types of granulation | Types of Compression
OR

Tablet preparation techniques -

1) Direct compression -
2) Dry granulation / Roller compaction / slugging
3) Wet granulation -

# Direct compression	# Dry granulation	# Wet granulation
· Weigh	· Weigh	· Weigh
⇓	⇓	⇓
· Sifting/sieving	· Sifting/sieving	· Sifting/sieving
⇓	⇓	⇓
· Mixing (blender)	· Mixing/blender	· Mixing/blender
⇓	⇓	⇓
· Lubrication	⊙ Slugging	Wet ⇐ ⊙ Granulation
⇓	⇓	Mass ⇒ ⊙ Sifting/milling
· Compression	⊙ Sifting/milling	⊙ Drying (60°c)
⇓	⇓	⊙ Sifting
· Tablets	· Lubrication	⇓
	⇓	· Lubrication
	· Compression	⇓
	⇓	· Compression
	· Tablets	⇓
		· Tablets

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Manufacturing defects in tablets-

1) Capping -
2) Picking & sticking -
3) mottling -
4) Weight variation -
5) Hardness variation -
6) Double impression -

1) Capping -
- Partial/Complete removal of top/bottom portion of the tablet.-

Reasons -
- High speed of the tablet machine.-
- High degree of Compression -
- Defective punches & dies -
- Granules are dry -

2) Picking & sticking -
- Picking - The material is removed/picked up by the upper punch from the surface of tablets -
- Sticking - The material sticks to the wall of the die. -

* 3) mottling - / Colour variation -
- Unequal distribution of colour on the surface of coloured tablets.

Reason -
- Migration of dye -
- Use of different colouration -

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4) Weight variation -
- Tablets don't have a uniform weight.-

5) Hardness variation -
- Tablets don't have a uniform hardness.-

* Hardness depends on the weight of material & space b/w upper & lower punches during the compression.-

6) Double impression -
- When the lower punch has a monogram during compression.
- Due to lower punch moves slightly upward.

** # IPQC test as per I.P. - [In process quality control test) OR [Evaluation of tablets] -

(1) Weight variation test => 20 tablets used for test -

	Weight	% Variation
i)	≤ 80mg	10%
ii)	> 80mg - < 250mg	7.5%
iii)	≥ 250 mg	5%

(2) Friability test => ≥ 6.5 gm / 7gm
=> 25 rpm & 4 minutes => 100 rotation -
- Weight => Loss => NMT 1%. (Not more than 1%) -

** - This test used only for "uncoated" tablets -

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③ Disintegration test -

* This test is not used for "chewable & sustain release" tablets -

a) Uncoated tablets ⇒ water, NMT 15 minutes -

b) Coated tablets ⇒ water, NMT 60 minutes -

c) Film coated tablets ⇒ water, NMT 30 minutes -

d) Enteric coated tablets ⇒ In 0.1M/N HCl solution for 2 hrs | 120 minutes no change in tablets [No shows sign of crack] 900ml, 37°C±2°C

⇓

at pH 6.8 phosphate buffer (in-intestine) - NMT - 60 mins

e) Dispersible tablets ⇒ 24°C to 26°C ⇒ NMT - 3 minutes

* Uniformity of dispersible tab. ⇒ 2 tab. - in 100 ml water ⟷ 2 hrs ⇓ # 29 Sieves

f) Effervescent tablets ⇒ 1 tab - in 250 ml water → 20°C - 30°C NMT - 5 minutes -

g) Soluble tablets [coated / film coated] → (10ml water)

· 15°C - 25°C → NMT - 3 minutes

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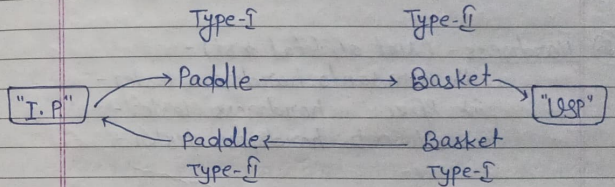
④ Dissolution test -

· The test is studied for a capsule or tablets -

· Apparatus - "As per IP" - "As per USP"

Type-I - Paddle, Type-II - Basket — Type-I - Basket, Type-II - Paddle.



⇒ Generally ⇒ 75 rpm & 900ml, 37°C

eg - Paracetamol tablets -

· Apparatus No. 1 -
· medium 900ml of phosphate buffer pH 5.8 -
· 50 rpm & 30 minutes -
· 37°C

- Telmisartan tablets -

· Apparatus No. 1 -
· medium 900ml of 0.1M HCl
· 75 rpm & 60 minutes -
· 37°C

{Pure drugs assay ± 2%}

[4,5 & 6 not SPQC] -

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(5) Content of active ingredient (Assay) -
⇒ ± 10 %.

· 10 tablets ⇒ Crass ⇒ 1 tab. blender ⇒ Dilution ⇒ Absorption.

(6) Uniformity of content -
· Each individual tablet less than 10mg drugs or < 10% -

(2) Hardness - (Not official test) -
i) Monsanto hardness tester -
ii) Pfizer hardness tester -
iii) Stoncob hardness tester -

Tablets coating -

* Purposes -
⊙ To mask the unpleasant taste & odour -
⊙ To improve the appearance of tablets -
⊙ To prevent the medicament from atmospheric effect -
⊙ To control the site of action of drugs (Enteric Coating)
⊙ To produce the sustained released product -

* Processes - / method of coating -
i) Pan Coating method -
ii) Press coating method -

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i) Pan - Coating method -
· In this technique the coating is done in a pan made up of copper or stainless steel. -
* The pan is roated with the help of an electric motor. -
* The tablets to be coated are placed in the pan. -
** Pan coating technique is used for -
a) Sugar coating -
b) Film coating -
c) Enteric coating -

ii) Press - Coating -
· In this technique the granules of coating material are prepared & a layer of coating material is placed on the preformed tablet in a "Oxycota - Rotary Tablet Machine."
⇓
* The whole operation is carried out automatically in a number of steps. -

i) Pan - Coating method -
a) Sugar Coating -
b) Film Coating -
c) Enteric Coating -

a) Sugar Coating - (3-4)
· Sugar coating is done by the pan coating method. -

Dusting powder = Starch + Tale + Powdered acacia

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* It is one of the oldest arts to mask the unpleasant flavours & tastes of medicaments.

* The various stages in the sugar coating process.
  - Sieving.
  - Sealing.
  - Sub-coating.
  - Syrup coating.
  - Finishing.
  - Polishing.

(ii) Film Coating - (1%)
- The tablets are coated by single or mixture of film forming polymers.
  eg.- Hydroxy-propyl methyl cellulose (HPMC).
  - Hydroxy ethyl methyl cellulose (HEMC).
  - Carbowax.
  - Poly-ethylene glycol 400 etc.

** Film coating is also used to make the tablets water proof before the sugar coating.

* Film coating can be enteric or non-enteric.

(iii) Enteric coating - (9%)
- Ensure that these tablets will not disintegrate in the stomach but pass through.
  ||
- Tablets get disintegrated in the intestines.

* The enteric coating of tablets is done in a rotating pan.

02/09/2022

* Solution of enteric coating material.
  eg.- Salol, cellulose acetate phthalate.
  - Shellac & its derivatives.

Micro-encapsulation.
- It is a process/technique by which thin coating can be applied to small particles of solid, droplets of liquid thus forming micro-capsules.

** The micro-capsules may consist of a single particle or groups of particles.

* It differs from other coating methods.
  ||
  Because
  micro-encapsulation process is used to coat the particles having a particle size range from several tenths of a μ (micron) to 5000μ.

* micro-encapsulation techniques are based on -
  - Chemical processes - (Chemical change).
  - Mechanical processes - (Physical change).

* Techniques are commonly used for micro-encapsulation.
  a) Pan-coating.
  b) Fluidised bed coating.
  c) Coacervation.
  d) Electrostatic deposition.
  e) Vacuum deposition.
  f) Polymerisation.
  g) Multiorifice centrifugal process.

(Tablet compression machine) or tablets

OR

Compression of granules into tablets [equipment & tablet tooling]-

* Granules are compressed into tablets in a machine known as a tablet making machine.-

* The dies, punches & their setup on compression machine is called tooling.-

* The various types of machine used in tablet compression-
  i. Single punch tablet machine ⇒ Hand operated small scale manufacturing ⇒ Electrically operated
  ii. multipunch tablet machine-
  iii. Rotary tablet machine- (rotatablimy) ⇒ large scale
  iv. Dry coat tablet machine- manufacturing

* Tablet compression machine is consist of-
  a. Hopper shoe-
  b. Lower punch-
  c. Upper punch-
  d. Capacity regulator-
  e. Ejection regulation-
  f. Die-
  g. Driving wheel-

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Liquid oral

Liquid

* These are the pharmaceutical dosage form to be administered orally in the form of-
  - Solution.-
  - Suspensions.-
  - Emulsions.-
  - Syrups.-
  - Elixir & many more

* Types of liquid oral dosage form-

Liquid oral

Monophasic liquids
eg. Syrups-
- Elixirs
- Solution-
- Linctus-

Biphasic liquids
eg.- Suspensions.-
- Emulsions.-

Monophasic liquids dosage forms

* Liquid preparation in which only one phase.-
* It is represented by true solution.-
* True solution-
  - It is a clear homogenous mixture that is prepared by dissolving dissolving a solid, liquid & gas in a liquid.-

* The component of solution present in large amount is known as "solvent"-
* The component of solution present in small amount is known as "~~solvent~~"-"solute"-

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Monophasic liquid dosage form -

* Internal
eg- Syrup -
- Elixir -
- Linctus -
- mixture -

* External
* i> Application on the skin -
eg- Lotion & Liniment -
* ii> Used in the mouth -
eg- Gargles, mouth wash, Throat paint -
* iii> Drop into body cavity -
eg- Ear drop, Nasal drop, Nasal spray & douche -

SYRUPS

* It is a Concentrated / nearly saturated solution of sucrose in purified water. - with / without flavouring & medicinal agents -
* {self preservative}
* The Concentration of sugar is "66.67% w/w" as per IP -
* The Concentration of sugar is "85% w/v" as per USP -
* The syrups are sweet viscous preparations -

* Classification of syrups -

a> Medicated syrup ⇒ Contains therapeutic agents -
b> Non - medicated syrup ⇒ Contains flavouring agents -
* Not medicinal substances -

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* "Advantages" -
i> Easily route of administration -
ii> Appropriate for any age group patient -
iii> Economical & safe to the patient -

* "Disadvantages" -
i> Delayed onset of action -
ii> Can't avoid 1st pass metabolism -
iii> Not suitable in emergency -
iv> Not suitable for unconscious patients -

* Formulation of syrup -
i> Excipients -
ii> method of preparation -

i> Excipients -
a> Vehicles - eg- Purified water -
b> Chemical stabilizers - eg- Prevent the crystallisation of sucrose -
eg- Glycerin, sorbitol & propylene glycol -

c> Preservatives - 66.67% w/w of sucrose have high osmotic pressure which prevents growth of micro-organisms (bacteria, fungi & moulds) -
** So no preservative is needed. -
* Generally - Benzoic acid, Sodium benzoate, - methyl paraben -

d> Colouring agents - eg- Coal tar dyes -
- Amaranth
e> Flavouring agents -
eg- Orange, vanilla, lemon, ginger & wild cherry -

*Inversion of sucrose ⇒ Phase exchange.
eg.- D-sucrose $\xrightarrow[\Delta]{\text{Excessive}}$ L-sucrose

2020 * Invert sugar ⇒ Dextrose + Fructose ⇓ Sucrose

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ii) method of preparation - (4- method)

a) Solution with heat -
b) Agitation without heat -
c) Addition of sucrose to liquid medicament -
d) Percolation method -

a) Solution with heat -

- Temperature of purified water is increased to 80°-85°
⇓
- Add sucrose with occasional (at random) stirring at dissolve
⇓
- Cool it & add more of purified water to make the required weight.-

Dis. advantage - Excessive heating may cause inversion of sucrose-

b) Agitation without heat ⇒ Syrup volatile substance containing -

* In this method stainless steel vessel or glass vessel is used.-
* The vessel should be large than the desired volume of syrup requid.-
⇓
* Then the ingredients according to the formulation are added to water & mixed-
⇓
* It is better to dissolve solid ingredients in the water & then add to syrup
⇓
* This results in easy mixing as sugar solution generally retards mixing-

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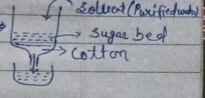
c) Addition of sucrose to liquid medicament -

* This method is generally used for fluid extracts.-
** But those substances which are soluble in alcohol-
* Precipitate out as soon as the addition of water -
* This method is no use.-

Limitation ⇒ Insoluble subs/particle not use in pharmacological action-

d) Percolation -

- The principle of percolation is used a sources bed is prepared & then water containing therapeutic agent is passed.-
⇓
- The sucrose bed should be coarse & shape of percolator -



ELIXIRS

* Elixirs are clear, sweetened, aromatic & "hydro-alcoholic" liquids intented for oral use.
* The main ingredients of elixirs are - ethyl alcohol (5-40%),
- water, glycerin -
- Propylene glycol -
- Flavouring agents -
- Colouring agents -
- Suitable preservative -
* Usually less sweet & less viscous than syrup -
* more stable than syrups -

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* Classification of ~~syrup~~ Elixirs -

a) Medicated elixirs ⇒ These are used for therapeutic effects
eg. - Antibiotics & anti-histamines -

b) Non-medicated elixirs ⇒ Not therapeutic effects -
* These only contain water, alcohol, sweetening & colouring agents -
eg. - Aromatic elixir perfumes -

* Formulation of elixirs -
i) Excipients -
ii) Method of preparation -

i) Excipients -
a) Vehicles -
b) Chemical stabilizers -
c) Preservatives -
d) Colouring agents -
e) Flavouring agents -

a) Vehicles - Water, alcohol, syrup, glycerin, sorbitol, propylene glycol -

* The water is used to dissolve the majority of ingredients of elixir. -
* The flavouring agents containing essential oils are easily soluble in alcohol - (5 - 40% v/v)

** Alcohol is used to make a clear solution. -

b) Chemical stabilizers -
· The various chemicals solvents are used in many elixirs to make stable elixirs -
eg. - Neomycin elixir → Adjust (pH 4-5)
- Citric acid

c) Colouring agents - eg. - Coal tar dyes
- Amaranth, Tartrazine
- Green S -

d) Flavouring agents - eg. - Lemon syrup -
- Orange syrup -
- Rasp berry syrup -

e) Preservatives -
* Prevents the growth of micro-organism
eg. - Benzoic acid & methyl paraben -

ii) Method of preparation -
· Dissolve the water-soluble ingredients in part of the water
⇓
· Dissolve the sucrose in it. -
⇓
· Dissolve the other ingredients in the alcohol (90%).
⇓
· The aqueous solution is then added to the alcohol solution with constant stirring & make up the volume with the solvent (vehicle) -

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⇓

- Sucrose ↑ viscosity but ↓ the solubility property of water

⇓

- So, in addition of viscosity-enhancing agents- eg.- Hydrophilic polymers
  - may be required to optimize the rheological properties of elixirs- ⇓
- Elixir should be brilliantly clear & therefore filtered.-

⇓

- If necessary, subjected to clarifying action of purified talc.-

* Advantages-	*Disadvantage-
• Better able to maintain both water soluble & alcohol soluble components in solution-	*Less effective than syrups in masking taste of medicated substances-
• Easily prepare by simple solution-	• Contains alcohol ↑ saline taste of bromides.-

* Coarse dispersion *
OR
Biphasic liquid dosage form
(Biphasic system | Heterogeneous system)-

- Emulsions:
  - Defined as at least two immiscible liquid phases, one of which is dispersed as globules in the other liquid phase.-

* Emulsions are thermodynamically unstable system-
* Globule diameter range 0.1um to 100um.-

Example- Milk, Rubber latex & crude oil etc-

*. Advantages-	*Dis-advantage-
. Improved bioavailability-	• Short shelf life-
. Topical use-	• Unstable-
. Mask the unpleasant taste-	
. Economical-	

* Types of emulsion-

a) Oil in water emulsion (o/w)- eg. Vanishing cream-
b) water in oil emulsion (w/o)- eg.- Cold cream-
c) multiple emulsion (o/w/o & w/o/w)-
d) micro emulsion

* Identification | evaluation of emulsion-

a) Dilution test-
b) Conductivity test-
c) Dye-solubility test (Staining test)-
d) Fluorescence test-
e) Cobalt. chloride test-

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* Theories of emulsification -

i) Electric double layer theory -
ii) Phase volume theory -
iii) Surface tension theory -
iv) Interfacial tension theory -
v) Hydration theory -

* Instability of emulsion -

i) Flocculation -
ii) Sedimention / Sedimentation -
iii) Phase inversion -
iv) Creaming -
v) Breaking -
vi) Coalescence -

* Formulation of emulsion -

i) Emulsifying agents / emulsifiers
ii) Preparation method -

i) Emulsifying agents -

a) Carbohydrate subs - eg - Acacia, Tragacanth, Agar - Pectin -
b) Protein subs. - eg - Gelatin, Egg yolk & Caesin -
c) Wetting agents - eg - Anionic, Cationic & Nonionic etc -

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ii) Preparation method -

a) Trituration method - i) Dry gum method -
ii) Wet gum method -
b) Bottle method -

Suspension

* Pharmaceutical dispersion in which insoluble solids (drugs) are suspended in a liquid medium. -

* Insoluble solids are p'cally useful agents. -
* Particle size 1 um to 50 um -

* Advantages -	* Disadvantages -
i) Stability -	ii) Sediment of solid -
ii) Choice of solvent -	iii) Microbial attack -
iii) Mask the taste -	iii) Oxidation & hydrolysis -
iv) Bio availability -	iv) Unpleasant taste or odour of drugs -
v) Ease of administration -	

* Types of suspension -

· Based on electrokinetic nature of solid particles -
a) Deflocculated suspension -
b) Flocculated suspension -

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* Evaluation of Suspension -

i) Sedimentation method - a) Sedimentation volume -
b) Degree of flocculation -
ii) Rheological method -
iii) Electrokinetic method -

* Factors affecting of suspension (Sedimentation) -

i) Brownian movement -
ii) Particle size -
iii) Viscosity of medium -
iv) Density of the medium -

* Formulation of suspension -

a) Excipients -
b) Manufacturing process -

a) Excipients -

i) Surfactants - eg. - Polysorbate - 80 / Tween 80 -
ii) Suspending agents - eg. - Acacia, tragacanth, Guar gum
iii) Solvents - eg. - Alcohol, glycerin, polypropylene
iv) Buffers & pH adjusting agents - eg. - Carbonates citrate Gluconate & phosphate
v) Preservatives - eg. Propylene glycol, benzoic acid
vi) Osmotic, colouring agents & flowering agents - Sweeting, Humectants & anti-Oxidant -

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b) Manufacturing process -

⊙ Insoluble drugs particles -
⇓
⊙ Addition of wetting agent / Surfatants & dispersion medium -
⇓
⊙ Uniform dispersion of deflocculated particles
⇓

(A) ⇓
⊙ Incorporation of structured vehicle.
⇓
⊙ Deflocculated suspension in structured vehicle as final product -

(B) ⇓
⊙ Addition of flocculating agent.
⇓
⊙ Flocculated suspension as final product -

(C) ⇓
⊙ Addition of flocculating agent.
⇓
⊙ Flocculated suspension
⇓
⊙ Incorporation of structure vehicle -
⇓
⊙ Flocculated suspension in structure vehicle as final product.

Filling & packing of liquid oral -

* The finished drug product filling & packing -

i) Gravimetric -
ii) Volumetric -
iii) Constant level -

19/09-

ii) Gravimetric-
· Containers are filled with liquids to a given weight.-

iii) Volumetric-
· Containers are filled with liquids to a given volume.-

iii) Constant level-
· Filled amount is verified by adjusting the height to which the container is to be filled.-

* Techniques of filling-

a) Vacuum filling-
b) Gravity vacuum filling-
c) Pressure vacuum filling-

Evaluation of liquid orals official in pharmacopoeia

i) Uniformity of content-
ii) Uniformity of weight/volume (w/v)-

i) Uniformity of content-
· Contain less than 10mg or less than 10% of active ingredients-

19/09-

* For oral liquids containing more than one active ingredient carry out the test for each active ingredient.

* Only after the content API in pooled sample of the preparation-

* Each of 10 containers taken at random using the method

⇓

· The individual values obtained lies 85% - 115% of the average value-

⇓

· If more than one individual value is outside the limits 85% - 115% of the average value

⇓

· Preparation fails-

* If any one individual value is outside the limit 75% - 125% of the average value

⇓

· Preparation fails-

* Repeat the determination-

· Another 20 containers taken at random (Total = 30 containers (10+20=30))

⇓

· NMT 3 individual values are outside the limit 85% - 115% - &
· NMT 1 individual values are outside the limit 75% - 125% -

19/09-

# Deflocculated suspension	# Flocculated suspension
• Uniform dispersion of particles -	• Unsightly sediment & clear supernatant layer
• Supernatant remains turbit	• Supernatant is clear -
• Particles experience repulsive forces -	• Particles experience attract forces -
• Particles exist as separate entities -	• Particles form loose aggregates -
• Rate of sedimentation is slow ↓	• Rate of sedimentation is high - ↓
sizes of particles are small	• sizes of particles are higher
• Particles settle independently & separately -	• Particles settle as floes -
• The sediment is closely packed & form a hard cake -	• Sediment is a loosely packed net work
• Bioavailability is relatively high -	• Bioavailability is Comparatively less -
• Represents the primary mini. (Potential energy curves).	• Represents the secondary minimum (Potential energy

Unit-3

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Capsules & pellets

Capsules

- Capsule are a solid dosage form in which the drug substance is enclosed in a water soluble shell/envelop

* A capsule shell is made from gelatin. -
* The capsules are available both as hard capsule & soft capsule. -
* Capsules are various shapes & capacities. -
* Single dose of active ingredients & intended for oral administration. -

* Advantages -
  - Easy to handle & carry -
- Unpleasant odour & taste can be administered by enclosing in tasteless shell. -
- It can be easily swallowed. -
- medicament release desired in gastro-intestinal trac
- made from gelatin & they are therapeutically inert. -
- Micro-capsulation provides the sustained released dosage form. -

* Disadvantages -
  - Hygroscopic drugs can't filled in capsules. They absorb water present in the capsule shell. -
- Conc. preparations which need previous dilution are unsuitable for capsule - (Unsuitable for use with liquid formulations) -

Types of capsule - (A) Hard gelatin capsules (RH4C) -
(B) Soft gelatin capsules (S4C) -

Hard gelatin capsule

28/09/022

* {Capsule ⇒ Cap + body}
* Used for administration of solid medicaments-

Ex. ## Production of hard gelatin capsule shells-

* The mechanism involved for production of hard gelatin capsule shells are -
  i) Dipping -
  ii) Spinning -
  iii) Drying -
  iv) Stripping & trimming -
  v) Joining -

* Preparation of the gelatin solution (dipping solution)-
  * Conc. of gelatin ⇒ 35-40% - & heated to 60-70°c -

i) Dipping -
  · Capsule shells are manufactured under strict climate condition by dipping pair (body & cap) of stainless steel pins.-

ii) Spinning -
  · After adsorption of the gelatin solution on to the surface of the pins, is rotated more times distribute the gelatin solution around the pins.-

iii) Drying -
  · The gelatin is dried & the pins are passed through several drying stages.-

iv) Stripping & trimming -
  · The capsule is stripped off the mould & trimmed to the proper length.-

* Isoelectric point - the pH at molecule carries "no net electrical charge"

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v) Joining -
  · The cap & body are joined to the pre-closed position using a "pre lock mechanisms"-

Ex. * Gelatins are used to manufacture capsule shell -

⊙ Dry bone	⊙ Calf skin	⊙ Pork skin
⇓ Bone meal	⇓ wash	⇓ wash
⊙ 5% HCl (10-15 days)	Lime 10%. (6-12 week)	1-5% HCl (10-30 hrs)
⇓	⇓	⇓
⊙ Lime 10% (4-8 weeks)		
⇓	⊙ Water wash (10-30 hours)	⊙ Acid removal
⊙ Lime removal		
⇓		
⊙ pH adjustment		
⇓	⇓	⇓

⊙ Hot water extraction
⇓ filter
⊙ Vacuum conc. -
⇓
⊙ cool to solidify -
⇓ air dry
⊙ mill to size

* HGC shell moisture ⇒ 12-16% -
* SGC shell moisture ⇒ 6-13% -

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Size of Capsules - [Capsule number & its capacity]

Capsule number/size	Approximate capacity in mg
000	950 mg -
00	650 mg -
0	450 mg -
1	300 mg -
2	250 mg -
3	200 mg -
4	150 mg -
5	100 mg -

Filling of hard gelatin capsule -

· The several type of filling machine in use in the p'cal industry -

· Excipients used in the filling of capsules ⇒ Diluents -
  ⇒ Absorbents -
  ⇒ Glidants -
  ⇒ Antidusting agents

i) Rectification - (Solution) -
ii) Separation of cap from body -
iii) Dosing of fill material -
iv) Replacement of cap & ejection of filled capsule -
v) Collection of capsules -

i) Rectification -

· The empty capsule are oriented so that all point the same direction that is body end downward -

ii) Separation of cap from body -

· This process depend on the difference in diameter b/w the cap & body -

29/09

* The diameter of cap is large to allow them to bodies into the lower portion. -

iii) Dosing of fill material -

· Various method / principle are used -
a. Auger fill principle -
b. Vibratory fill principle -
c. Piston - tamp principle -
d. Vacuum fill principle -

iv) Replacement of cap & ejection of filled capsule -

· The cap & body dushing portion are rejoined. -

* Capsule filling method / HGC filling method -

a. manual filling -
b. Hand filling machine -
c. Semi - automatic machine -
d. Fully automatic capsule filling machine -

Finishing of HGC -

· The commonly used step for production / producing finished capsule are follow

i) Cloth dusting -
ii) Polishing -
iii) Brushing -
iv) Sorting -

29/09-

i) Cloth dusting-
· It is manual method in which small number of capsule are rubbed with cloth.-

ii) Polishing-
· Special pan used for polishing the filled capsule.-
* These pan lined with poly-urethane cloth which remove the dust.-

iii) Brushing-
· In this method remove the dust from capsule shell.-
* This process is ~~in~~ assisted under vaccum.-

iv) Sorting-
· It is needed to separate the damaged & imperfect capsule.-
* Used equipment - eg. Rotosort-

Special techniques of formulation of HGC-

a) Imprinting-
b) Solubility-
c) Separation of incompatible material-
d) Filling of conventional two piece gelatin capsule with liquid & semisolid-

29/09-

a) Imprinting-
· It is method by which product identification information can be placed upon each capsule.-
* Imprinting operation is best performed on empty capsule.-

b) Solubility-
· For special purpose capsule attempt to retard solubility in some manner-
i) Formaling treatment => modify the solubility of gelatin capsule-
ii) Various coating => modify solubility character-

c) Separation of incompatible material-
· Involving two phase - i) One phase - Suitable coated filled into the capsule
ii) Second phase - Powder fill is added -

d) Filling of conventional two piece gelatin capsule with liquid & semisolid-

⇓

· The formulation used for filling are usually semi-solid at ambient temp-
* They are thixo-tropic formulation in which the shear developed in filling - (High viscosity)
* When shear is absent prevent leakage after filling.-

29/09/-

Manufacturing defect of HGC-

- Shell surface not smooth-
- Opacity not proper-
- Empty capsules after the filling stage-
- The foreign matter inside the capsule-
- Colour variation & non-uniformity of appearance
- Capsule may be cracks, breaks & splits-

In process quality control (IPQC) for HGC-

i) Weight variation / uniformity of weight test-
ii) Disintegration test-
iii) Content of active ingredients - (Assay) -
iv) uniformity of content (CU)-

i) Weight variation / uniformity of weight test-

Average weight of capsule contents.	Percentage deviation
< 300mg	10%.
≥ 300mg	7.5%.

ii) Disintegration test - HGC-

- Water (medium) -
- Operate the apparatus for 30 minutes -

30/09/-

iii) Content of active ingredients - (Assay) -
± 10%.

- This range is based on the requirement that 20 capsules are used in the assay.-

* NLT 5 - capsules are used -

iv) Uniformity of content -

- This test is applicable to capsules that active ingredient contain less than 10mg / 10% w/w -

** For capsules - Containg more than one active ingredient

- Test for each active ingredient that corresponds to the afore-mentioned conditions -

** Test is not applicable for capsules containing multivitamins & trace elements -

* 10 capsules taken at random -

- NMT 1 - individual values outside the 85% - 115% -
- Not any (none) individual values outside the 75% - 125%

* If 2/3 - individual value are outside 85% - 115%.

- 20 capsules another taken (Total = 30 capsule (none))
- NMT 3 - individual values outside the 85% - 115% -
- Not any individual values outside 75% - 125%.

30/09-

Final product quality control tests for HGC-/Capsule

i) Appearance ⇒ Visual or electronic inspection-
ii) Size & shape ⇒ Rang from 000 to 5 -
iii) Disintegration-
iv) Dissolution test - as per USP.
- Type-I - Basket
- Type-II - Paddle-

Soft gelatin capsules (SGC)-

- These are used for administration of liquid medicament
* Available in - Round, Oval & tube like shapes.-
* They are made from gelatin-
* Gelatin is plasticized by the addition of glycerin & sorbitol etc-
** SGC shell may contain a preservative to prevent the growth of microb & fungi-
* These are used to enclose liquid medicaments- eg.- Oils, suspensions, food conc. & ophthalmic product

Nature of Capsule shell-

- Basically composed of gelatin, plasticizer & water
- The gelatin is USP grade with additional specification required-

01/10-

- Bloom & gel strength-
- Viscosity of gelatin determined on a 6⅔% conc. of gelatin in water at 60°C-
* The viscosity for gelatin can ranges from 25-45 millipoise-
- Iron is always present in the raw gelatin-
* NMT 15PPM of this elements-

Capsule Content-

- Content may be-

i) liquid-
ii) Combination of miscible liquids-
iii) Solution of solid in a liquids-
iv) Suspension of solid in liquids-
* It can be a liquid like a volatile oil composition- eg- Arachis oil, aromatic oil, aliphatic hydrocarbon, ethers, esters & alcohols-
** Liquids are important part of capsule content-

Size & shape of SGC-

- The maximum capsule size & shape for convenient oral use in human-
- 20 minimum oblong-
- 16 minimum oval-
- 9 minimum round-

03/10-

Importance of base adsorption:-

$$\text{Base adsorption} = \frac{\text{Weight of base}}{\text{Weight of solid}}$$

- In the formulation of suspension for soft gelatin encapsulation-
- Basic information must be developed to determine minimum capsule size.-
- Base adsorption is expressed as the number of gram of liquid required to produce a capsulatable mixture-

* The base adsorption of solid effect/influence by-

i) Particle size & shape-
ii) Physical state (Amorphous or crystalline)-
iii) Density, moisture content, its oleophylic & hydrophilic nature-

* Determination of base adsorption = $\frac{\text{Weight of base}}{\text{Weight of solid}}$

Minim per gram factor (M/g)-

- The base adsorptions used to determine the "minim per gram" factor (M/g) of the solid-

* Minim per gram factor (M/g) = $(BA + S) \times \frac{V}{W}$

where; BA = Weight of the liquid base-
S = Weight of solid base-
W = weight of mixture - (Per cubic cm)

V = 16.23 minim,

Production of SGC-

i) Plate process -
ii) Rotary die process -
iii) Reciprocating die process -
iv) Accogel capsule filling machine-

i) Plate process-

- Place the gelatin sheet over a die plate containing numerous die pockets.
- Vaccum to draw the sheet into the die poekets -
- Fill the poekets with liquid or paste-
- Place another gelatin sheet over the filled pockets-
- Sandwich under a die press-
- The capsules are formed & cut out.-

ii) Rotary die process-

It is having two hoppers & two rotating dies-

- In this machine the soft gelatin capsules are prepared & then filled immediately with liquid medicaments-
- Liquid mixture is placed in one hopper & the liquid medicament placed in other hopper-
- Two rotating dies rotate in opposite directions-

iii) Reciprocating die process-

· This machine produces capsule completely automatically -

⇓

By leading two films of gelatin b/w a set of vertical dies. -

iv) Accogel capsule filling machine-

· This is another rotary process involving a measuring roll -

⇓

· Die roll & sealling roll-

* Formulation of filling material of SEC-

· following criteria

i) Compatibility with capsule shell-
ii) Ability to dissolve the drugs -
iii) Rate of dispersion in the GI fluid-
iv) Ability to the bioavailability of drugs-

* Types of filling-/Bases-

a) Hydrophilic liquids- eg PEG-400-
b) Lipophilic liquid - eg- steroids & vit. D -
c) Micro-emulsion system -
d) Emulsifying oil - eg- Poly-oxyethylene -
e) Suspension - eg-

In process & final product quality control test-

* In process testing - During the encapsulation process-

i) Gel ribbon thickness -
ii) Gel seal thickness -
iii) Capsul shell weight -
iv) Gel shell moisture level-

* Finished product testing -

· Special quality control test-

a) Seal thickness -
b) Total moisture test -
c) Capsule rupture test -
d) Determination of freezing & high temperature test

* Test parameter almost same as hard capsule- like- i) Appearance -
ii) Size & shape -
iii) Disintegration test -
iv) Dissolution test -

Packaging & store of capsule -

· The main aim -

i) To prevent contamination -
ii) To prevent loss or gain of moisture during long term storage -

16/10-

** Many plastic container & various packing technology are used-
- like - Blister packaging-
- Strip packaging-

* Storage-
- Long time period require proper maintenance of temp & humidity - (for HGC)-

* Relative humidity (%) ⇒ 35% → 65% (Best ⇒ 50%)-
* Temp. (°C) ⇒ 15°C → 25°C (Best ⇒ 20°C)-

* Capsule physical stability-
- Effect of temp. & humidity on the products-
- Effect of temp & humidity on the SGC-
  - RH ⇒ 20% → 30%
  - Temp ⇒ 21°C → 24%
- Physical stability test in their own lab-
- Temp ⇒ 21-24°C & Humidity ⇒ 60%.
  ⇓ Effect on Capsule shell-
- Capsule become softer, tackier & bloated-
- Temp ⇒ >24°C & Humidity ⇒ > 45%
  ⇓ Effect on Capsule shell-
- More rapid effect on unprotected Capsule- melt & fuse together

16/10-

Application of soft gelatin Capsule [SGC]-
- They permit liquid medications to become easily-
- Accuracy & uniformity of dosage-
- Improve the physiologic availability of drugs-
  ⇓ Because
  Capsule contain the drug in liquid form-
- Orally administered drugs-

Differentiation b/w Hard gelatin capsules & Soft GC-

(HGC)	(SGC)
• The HGC shell consists of two parts- a) Body, b) Cap	• The SGC shell becomes a single unit after sealing the two halves of the cap
• They are cylindrical in shape	• They are available in- Round, Oval & tube shape
• The contents of HGC- ⇓ medicaments in the form of powder, beads or granules-	• The content of SGC- ⇓ medicaments in the form of liquids or solids dissolved in suitable excipients- (like- paste)-
• These are prepared from gelatin, titanium dioxide, colouring agent & plasticizer	• These are prepared from gelatin, plasticizer & preservative-
• Capsules are sealed after they are filled-	• filling & sealing of SGC are done in a combined operation on machines-

Pellet # · Size = 0.5 - 1.5 mm - 16/10 -

- Pellets are small, free flowing & spherical particles
- manufactured by the agglomeration of fine powders of the drugs substances with suitable excipient -

- Advantages -
  - Uniformity of dose -
  - Spheres have excellent flow properties -
  - Prevention of dust formation -
  - Controlled release profile -
- Its advantages -
  - Complicated manufacturing process -
  - High cost of manf -
  - High equipment required
  - It is difficult to Compress -

Formulation requirements -

(A) Active pharmaceutical ingredient - [API] -
(B) Excipient - i) Binder - [Agglomeration inducers / Bridging
ii) Granulating fluid -
iii) Spheronizing enhancer -
iv) Filler -
v) Plasticizer -
vi) Lubricant -
vii) Separating agents -
viii) Surfactant -
ix) pH adjusters -
x) Release modifiers -
xi) Organoleptic agents → Flavoring agent -
→ Sweetening agent -
→ Coloring agent -

(A) API -
- APIs are used in different drugs development like - Immediate release -
  - Sustained release -

(B) Excipients -

i) Binder / Agglomerating inducers / Bridging agents -
- Bind powder & maintain integrity -
eg - Gelatin, Sucrose, Starch, HPC, HPMC, MC & PVP -

ii) Granulating fluid -
- Wet mass prepared is the most crucial parameter -
eg - Alcoholic / hydro-alcoholic systems -
- Ethyl ether, Dilute acetic acid -
- Isopropyl alcohol -

iii) Spheronizing enhancer -
- formulation aids that improve the production -
eg - MCC & Sodium CMC -

iv) Filler -
- Form the bulk of the material - (70% - 80%) -
eg - MCC, GMS (Glyceryl mono stearate), Avicel PH 101, & Starch Rx 1500 -

16/10-

v) Plasticizer-
· Improve the flexibility of polymers by reducing the tensile strength-
eg.- Glycerol, propylene glycol, dimethyl & diethyl, dibutyl phthalate-

vi) Lubricant - Rarely used-
eg.- Calcium stearate, Glycerin, PEG, Mg stearate-

vii) Separating agents-
· Adsorbed on the surface & promote the separation -
eg.- kaolin, talc, silicon dioxide-

viii) Surfactant -
· Improve wettability-

ix) ~~viii)~~ pH adjusters -
eg. Citrate & phosphate-

x) Release modifiers-
eg.- Ethyl cellulose, Carnauba wax & shellac -

xi) Organoleptic agents => Flavouring agent - Flavours change
=> Sweetening agent -eg.- Sucrose, dextrose, fructose, glucose, liquid glucose & maltose-
=> Colouring agent- eg.- Titanium dioxide-

NOTE

· It is process in which formation of pellet by agglomeration method is called pelletization - 16/10-

II. Pelletization process-
· 3 Consecutive regions-
i) Nucleation -
ii) Transition -
iii) Ball growth -

· Based on the experiments on the mechanism of pellet formation & growth-

i) Nucleation -
· It is a stage of pelletization process-
· Nuclear formation depends upon the → size of the particles, the moisture content;
→ The viscosity of the binding particles-
→ The wettability of the substrate -
→ The processing conditions -
→ The tumbling & drying rates-

ii) Transition phase -
· The growth mechanisms affecting are coalescence & layering-
· Coalescence ⇒ formation of large-sized particles by random collision -
· Layering ⇒ The successive addition of fragments-

iii) Ball growth phase-
· It is the abrasion transfer which involves the transfer of materials -

16/10-

Pelletization techniques-

i) Extrusion spheronization -
ii) Layering technique -
iii) Cryopelletization -
iv) Hot melt extrusion -
v) Freeze pelletization -
vi) Multiple unit pellet system (MUPS) -

{ imp ll }

i) Extrusion spheronization -

- Dry mixing
- Wet massing
- Extrusion
- Spheronization
- Drying
- Screening

ii) Layering technique -

a) Solution/Suspension layering -
b) Powder layering -

iii) Cryopelletization -

In this technique liquid nitrogen at -196°C is used -

16/10-

iv) Hot melt extrusion -

- Following steps -

a) Feeding of the extruder through a hopper -
b) Mixing, grinding & kneading -
c) Flow through the die -
d) Extrusion from the die & further downstream processing

v) Freeze pelletization -

- A molten-solid carrier in which the drug is uniformly dispersed is allowed to enter as tiny droplets -
- Melting point of solid carrier used below 100°C -

vi) Multiple unit pellet system (MUPS) - 2 steps -

a) Pellets manufacturing -
b) Tablet containing pellets manufacturing -

Equipments for manufacture of pellet -

i) mixer like Sigma blade mixer, hexagonal mixer -
ii) Drying equipment like fluidized bed dryer, spray dry
iii) Fluidized bed processor -
iv) Freeze drying -
v) Spheronizer -
vi) Coating pan, Compression machine -

*Unit- IV *

Parentral products & Ophthalmic preparation

Parentral products

- Those are p'cal products that are given by other than oral routes-

* Example- Transfusion fluids & injections-

* These are the sterile solution / suspension of drugs in aqueous / oily vehicle-
* Sterile, isotonic & free from foreign particles-

* Types of parentral preparation-

1) Solution / Emulsions of medicaments suitable for injections-
2) Sterile solids-
3) Sterile suspensions-
4) Transfusion fluids-

1) Solution / Emulsions of medicaments suitable for injection-

⇓

- Commonly called as injections.-
- Supplied in single dose containers or multiple dose containers.-
- Volume ⇒ 0.5 ml to litere
- Example-
  - Atropine sulphate injection-
  - Dextrose injection-

2) Sterile solids-
- Not stable in solution preparation-

* Supplied as dry sterile solids which are dissolved in a suitable solvent immediately before its administration-
eg- Benzyl penicillin-G-sodium injection-

3) Sterile ~~solids~~ suspension-
- Administered by "intra-muscular route- eg.- Sterile hydro-cortisone acetate suspension-
- Sterile chloramphenicol suspension-

4) Transfusion fluids-
- Administered by "intra-venous"

* Generally used - Nutrition-
- Maintain the electrolyte balance-
eg.- Ringer solution -
- Dextrose solution-
- Sodium chloride injection-

* Advantage-
- Onset of action is quick-
- 100% bioavailability-
- They are free from pyrogen-
- Administration of unconscious patients-
- Not take oral administration-
- Low toxicity as compared to solid dosage forms-
- No chance of missing dose-

* Limitation / disadvantage-
- Cause pain at the site of injection-
- Chance of sensitivity reaction / allergic rxn of a drug by a individual-
- Requirement of aseptic technique in production-
- Requirement of trained personnel for administration-
- Highly risky-

* Preformulation factors & essential requirements-
i) Stability ⇒ Physical & Chemical stability-
ii) Sterility ⇒ Free from all types of micro-organisms-
iii) Free from pyrogen ⇒ Free from toxin & pyrogens-
iv) Free from foreign particles ⇒ Pass the clarity test-
v) Isotonicity ⇒ with plasma & body fluids-
vi) Specific gravity ⇒ Same specific of body fluid-
vii) Chemical purity ⇒ Free from chemical impurities

* Route of administration of parenteral products-
i) Intra-dermal injection (intra-cutaneous)-
ii) Hypo-dermic injection (Sub-cutaneous)-
iii) Intra-muscular injection (I.M.)-
iv) Intra-venous injection (I.V.)-
v) Intra-arterial injection-
vi) Intra-Cardiac injection-
vii) Intra-thecal injection-

viii) Intra-cisternal injections-
ix) Peri-dural injections-
x) Intra-artheular injections-
xi) Intra-cerebral injections-

* Essential requirements for formulation-
• make a stable preparation-

1) Vehicles - i) Aqueous vehicles-
ii) Non-aqueous vehicles-

2) Adjuvants-
i) Solubilising agents-
ii) Stabilizers-
iii) Buffering agents-
iv) Anti-bacterial agents-
v) Chelating agents-
vi) Suspending, emulsifying & wetting agents
vii) Tonicity factors-

1) Vehicles-
• Two types of vehicles which are commonly used for the preparation of injections

i) Aqueous vehicles-
• Water is used as vehicle for majority of injections-

• Because - Tolerated well by the body-
- Safest to administer-

* Aqueous vehicle used are-
i) water for injection-
ii) water for injection free from CO_2-
iii) water for injection free from dissolved air-

* water for injection ⇒ sterial water-
⇒ free from volatile, non-volatile impurities & pyrogens-

* Pyrogens are by-product of bacterial metabolism

ii) Non-aqueous vehicles-
• Commonly used non-aqueous vehicles are oil & alcohols-
• Oil - eg. - arachis oil, cotton-seed oil, almond oil, & sesame oil-
• Alcohols - eg. - Propylene glycol & glycerin-

(2) Adjuvants-
• Increase the stability/quality of the product.-

i) Solubiling agents-
• ↑ the solubility of drugs-
eg. - Surfactant & co-solvents-

iii) Stabilizers-
· Prevent by oxidation & hydrolysis-
eg- Thiourea, ascorbic acid, & sodium meta-bi-sulphite-

iii) Buffering agents-
· Prevent by change in pH-
eg- Citric acid & sodium citrate-
· Acetic acid & sodium acetate-

iv) Anti-bacterial agents- [Preservatives]-
· Prevent the growth of micro-organisms during storage.-

v) Chelating agents-
· Formation of complex with heavy metal ions-
eg- EDTA [Ethylene diamine tetra acetic acids]-

vi) Suspending, emulsifying & wetting agents-
· Improve the viscosity
eg- methyl cellulose, acacia, gellatin etc-

vii) Tonicity factors-
· Isotonic with blood plasma & other body fluids-
eg- NaCl, dextrose & boric acid-
(0.9%) (5%) (1.9%)-

* Importance of iso-tonicity-

* Iso-tonicity- iso ⇒ same, tonicity ⇒ concentration-
· Two solutions have same osmotic pressure across the semi-permeable membrane.-

* Iso-tonic solution-
* Hypertonic solution-
* Hypo tonic solution.
⇒ Types of tonicity-

* Isotonicity is important for parentral preparation because-
· The possibility of product penetrating the RBC & reduced haemolysis.-

* Hypertonic solution ⇒ Swelling
* Hypotonic solution ⇒ Haemolysis-
⇒ Cause-

* Production procedure-

· Material management · Raw material & API-
· Packaging material-
⇓
· Manufacturing requirement.
⇓
· Finishing products [Labeling & packing]-
⇓
Ware-housing [Storage of products)-

02/11/-

* Involved step-

i) Cleaning of containers, closures & equipment-
ii) Collection of materials-
iii) Preparation of parentral products-
iv) Filtration
v) Filling the preparation in final containers-
vi) Sealing the containers-
vii) Sterilisation-
viii) Evaluation of parentral product-
ix) Labelling & packing-

* Production facilities & Controls-

· Divided into five sections-

a) Clean-up area-
b) Preparation area-
c) Aseptic area-
d) Quarantine area-
e) Finishing & packaging area-

* Aseptic processing-

It is a process by which sterile (aseptic) product is packaged in a sterile container maintain sterility-

* Sterility => Flash-heating process-

02/11/-

· Raw material
⇓
· Continuous heating
⇓ Hold tube
· Continuous cooling
⇓
· Hold tank
⇓
Package material → · Aseptic filler
⇓
· Finished product

Aseptic Zone

* Formulation of injection- [Solution & Suspension]

· Sterilization & milling of active ingredients-
⇓
· Sterilization of vehicle-
⇓
· Aseptic wetting & dispersion of the active ingredients-
⇓
· Aseptic milling of the bulk suspension-
⇓
· Aseptic filling of the bulk suspension in suitable containers-

02/11-

* Formulation of sterile powder-
  - Due to instability in water-

eg.- Penicillins, Barbiturates & benzocain-

* Sterile water for injection is supplied with dry powders to make solution/suspension for injection

* Sterile powders are prepared by-
  i) Sterile re-crystallization method-
  ii) Lyophilization method-
  iii) Spray drying method-

* Formulation of large volume parentral (LVP)-

- The group of sterile products are known LVP-
- Administered by "intra-venous" [infusion fluids"]

* Single dose injecting volume ⇒ 100ml / more than 100ml-

* Example of LVP- Infusion fluid-[Basic nutrition-dextrose injection, fluid replacement therapy- normal saline]-
- Total parentral nutrition solution (TPN)-
- Intra-venous anti-biotics-
- Dialysis fluid-
- Irrigation solution-

02/11-

* LVP are mostly clear solutions-
  Except- Oil in water emulsion (o/w)-

* Formulation of lyophilized products-

* Lyophilization / freeze-drying-
  - It is a process in which water is removed from a product-

* The process consists of 3- separate processes-
  i) Freezing-
  ii) Primary drying (Sublimation)-
  iii) Secondary drying (desorption)-

* Containers & Closures selection-/use-

- 3- types of glasses are used for the preparation of parentral product-

1) Type-I-glass- known as neutral glass-
   - High resistance to hydrolysis & weathering-
2) Type-II glass- known as sulphated glass-
   - High resistance to hydrolytic-
3) Type-III glass- known as soda glass-
   - Little resistance to hydrolysis-
   - only used for non-aqueous preparation

* Containers made from type II / type III glass used once only for parentral products.-

* Plastic & rubber packaging used in parentral prep

* Filling & sealing of -

a) Ampoules -
. These are thin-walled glass containers.

* The contents are withdrawn after rupture of the glass.-
* These are great packaging for a variety of drugs.
* The packing is 100% tamper proof.-
* The break system OPC (One-point cut)-
* The colour break ring offer consistent breaking fea
* These are wide varity of ampoule types from 0.5ml to 50ml volume-

* Filling by - Graveity, pressure & vacuum filling devices-
* Ampoules may be closed by melting portion of the glass of neck from - Tip-seals -
- Pull seals-

b) Vials & infusion bottle -
- Two method -
i) Volumetric filling method -
ii) Time/pressure filling method-

* Volumetric filling machines have "pistons or peri-staltic pumps".-
⇓
These are most common used method.-

* Time filling is used for filling of sterile liquids.

Quality control tests of parentral products-

. The finished parenteral products tests-
1) Sterility test -
2) Clarity test -
3) Leakage test -
4) Pyrogen test -
5) Assay -

1) Sterility test -

. All the parentral preparations which are supplied in sterile form -
* Test for sterility is done by presence of viable forms of bacteria, fungi & yeast in parentral preparation -

02/11-

* The test for sterility by-
i) membrane filtration method-
ii) Direct inoculation method-

* steps involved in sterility testing-

a) Selection of the sample size-
b) Selection of the quantity of product to be used-
c) Method of testing-
d) Observation & results-

(2) Clarity test-

· To ensure that the parenteral products are free from foreign particles.-

*· Coulter- counter method/instrument used-

(3) Leakage test-

* This test is performed only for ampoules-
* This test is performed in vacuum chamber-

** Vials & bottle are not subjected to this test-
* Because- rubber are flexibility.

02/11-

(4) Pyrogen test-

* Test is done as per I.P. 1996 to check the presence or absence of pyrogen in all aqueous parenteral preparations.-
* measurement of the rise in the body temperature-

* Pyrogens are polysaccharides & thermostable.-

* materials required for the test
i) Temperature recording device-
ii) Glass wares-
iii) Syringes & needles-
iv) 3- healthy adult rabbits-

(5) Assay-

* Performed according to the monograph method of parenteral preparation-

* It is done to check the quantity of medicament present in the parenteral preparation-

* Progen testing *

* Components-

(A) Introduction-
(B) Principle-
(C) material required for the test-
(D) method-
(E) Interpretation of results-

(6) # Ophthalmic preparation # 03/11-

* These are the sterile products.-
* Instillation (drip/drops) into the eye in the space b/w the eye lids & eye balls.-

* Ophthalmic products include-
i) Eye drops-
ii) Eye lotions-
iii) Eye ointments-
iv) Eye suspensions ⇒ Not commonly used.-
v) Contact lens solution-

* Essential characteristics of different ophthalmic preparations- (formulation considerations)-
a) Foreign particles-
b) Viscosity-
c) Tonicity-
d) pH of the preparation-
e) Sterility-
f) Surface activity-
* Tears have a pH about 7.4-

a) Foreign particles-

All the ophthalmic products should be clear & free from foreign particles, fibres & filaments.-

* Very carefully by passing through bacterial proof filters.- eg.- membrane filters-
- Sintered glass filters-

b) Viscosity -
· Prolong the contact time of the drug in the eye.-
* Various thickening agents are added in the ophthalmic preparations -
eg.- Polyvinyl alcohol, polyethylene glycol, methyl cellulose & carboxy methyl cellulose etc-

** Thickening agents are not used in eye drops & eye lotions -

c) Tonicity -
· Isotonic with lachrymal secretion -
eg.- 1.9% boric acid -
- Sodium acid phosphate buffer -

d) pH of the preparation -
· Important role in the therapeutic activity, solubility, stability & comfort to the patient.-
* Tears pH ⇒ 7.4 -

e) Sterility - [Preservative] -
· Prevent the microbial growth in ophthalmic preparation -

f) Surface activity [Surfactants] -
eg.- Benz-alkonium chloride, polysorbate 20, polysorbate 80 etc-

* Formulation -

(A) Eye drops -

* Eye drops are sterile aqueous/oily solution/suspensions of drugs -
* They are instilled into the eye with a dropper.-
* They are used both for diagnostic & therapeutic purposes -
* Drugs act on the anterior segment of the eye.-
* Eye drops are prepared in 4- stage -
i) Preparation of bactericidal & fungicidal vehicle -
ii) Preparation of solution of medicaments & adjuvants -
iii) Clarification -
iv) Sterilation -

(2) Eye lotions -

* These are the sterile aqueous solution used for washing ~~for~~ of eyes.-
* The eye lotions are supplied in conc. form & are required to be diluted with warm water immediately before use.-
* Eye lotions are simple solution -
* Not be stored for more than two days as the lotion.-

* They are iso-osmotic with tears -
* Nacl eye lotion & $NaHCO_3$ eye lotion are commonly used.-

(3) Eye Ointments-

- Eye ointments are sterile preparations -
- Application to the eye.-
* The ointment base selected for an eye-ointment must be non-irritating to the eye.-
* Eye ointment melt near to the body temperature
* Ointment base- eg.- Yellow soft paraffin-
  - Liquid paraffin
  - Wool fat-

* method of preparation-

i) Preparation of bactericidal & fungicidal vehicle-
ii) Preparation of solution of medicament & adjuvants-
iii) Clarification-
iv) Sterilisation-
v) Container-

* Labelling & containers-

i) The name of the pharmaceutical product-
ii) The name of the active ingredients-

03/11-

iii) The conc. of the active ingredients & the amount
iv) The batch number
v) Date of mfg & date of expiry -
vi) Direction for use & warnings -
vii) Name & address of the mfg.-

* Containers-

- Ophthalmic liquid products were packed in glass containers fitted with eye dropper

* Plastic containers fitted with nozzles -

(4) * Evaluation of ophthalmic products-

a) Sterility -
b) Anti-microbial preservatives -
c) Uniformity of dosage units -
d) Uniformity in Containers-
e) Leachable & extractables -
f) Container closure integrity-
g) Viscosity -
h) Antioxidant content -
i) Particle size & particle size distribution -

03/11-

a) Sterility-
· Standard requirements for ophthalmic preparation-

b) Anti-microbial preservatives-
· Preservative in multi unit products should be established.-

c) Uniformity of dosage units-
· Performed for single dose containers-
· Performed uniformity / weight variation-

d) Uniformity in Containers-
· To ensure the drug prod integrity-
· To ensure uniformity of the finished product

e) Leachable & extractables-
· Quality & purity of the drug product-

f) Container closure integrity-
· Prevent contamination or loss of contents (drugs)-

g) Viscosity-
· Residence time of the product-

03/11-

h) Anti-oxidant content-
· Prevent the oxidation-
· impurity testing-
* ↑ the stability & ↑ shelf life of product-

i) Particle size & particle size distribution-
· stability testing-
* Drop size for ophthalmic drop ⇒ "20-70 µm"-
* Maintain the product self life.-

Unit - V^th

21/10/2022

Cosmetics, Pharmaceutical aerosols & packaging-materials science

Cosmetics

- Cosmetics are the products used for the purpose of cleansing, beautifying & alternating one's appearance.

* Cosmetics is one of the branch of "Cosmetology"-

* Cosmetology -
  - It is the study & application of beauty treatments-

* Generally, Cosmetics are external preparations which are applied on the external parts the body

* Cosmetics are considered as essential components in life.-

* The most popular cosmetics are-"hair dyes"-
  -"Powders"-
  -"Creams"-

* Examples of cosmetics-
  - Creams (cold & vanishing cream)

tooth pastes, shampoos, hair dyes, sunscreens & lipsticks-

- Sunscreen (Sun-cream, Sun-block, Suntan lotion)

21/10-

* Classification of Cosmetics-
A. Skin Cosmetics -
B. Hair Cosmetics -
C. Nail Cosmetics -
D. Cosmetic for hygiene purpose-
(Sanitation)

Formulation & preparation of the following Cosmetic preparations -

① Lipsticks-
· Dispersion of the colouring matter base of suitable blend of oil, fats & waxes with suitable perfumes & flavours-

Formulation of lipstick -

Ingredients	Examples
i) The solid components/waxes	⇒ White bees wax, & hard paraffin
ii) The liquid components	⇒ Mineral oil, castor oils & glycol
iii) The softening components	⇒ Anhydrous lanoline & lecithin-
iv) The coloring agents	⇒ Carmine & pigmented stain-
v) Perfumes	⇒ Rose oil, Cinnamon oil -
vi) Preservatives	⇒ Parabens -
vii) Anti-oxidants	⇒ BHA, BHT & tocopherol etc-
viii) Flavouring agents	⇒ Cinnamonial & spearmint oil

Preparation of lipsticks-
· Successful preparation of lipstick depend upon of sufficient dispersion of the lake colours in the lipstick mass.-

· Take castor oil, lanoline alcohol, oleyl alcohol in a beaker (A) containing dyes & pigments-
⇓
· Heat the above mixture to 65°C-
⇓
· In another beaker (B) take remaining indredients Heat to 65°C-
⇓
· Then added the contents of beaker (A) to beaker (B) by vigorous stirring-
⇓
· Then this solution is added to molds-

* Evaluation- i) melting point-
ii) Breaking point-
iii) force of application-
iv) stability-
v) Microbial testing-

② Shampoos-
· It is a viscous cosmetic preparation with synthetic detergent used for washing hair, is called shampoo-

21/10-

* Formulation of shampoo -

Ingredients	Examples -
i) Surfactants	=> Alkyl sulphates, alkyl ether sulphate
ii) Foam booster	=> Mono-ethanol-amides, Lauramides DEA-
iii) Germicides & anti-dandruff agent	=> Selenium sulphide, Cadmium sulph, Benzalko-nium chloride -
iv) Preservatives	=> P-hydroxyl benzoic acid, phenyl mercuric nitrate -
v) Thickeners	=> methyl cellulose, polyvinyl alcohol -
vi) Perfuming agents	=> Herbal fruits -
vii) Colour	=> FD & C dye -

* Preparation of shampoo -

· Simple procedure ~~in the~~ is involved in the preparation of shampoo -

· All the ingredients are weighed contents able taken the solid base will mixed -

⇓

· Liquid base mixed separately -

⇓

· These mixture wer ~~ffurate~~ & mixing together to get a fine shampoo. -

* Evaluation of shampoo -

i) Evaluation of safety -
ii) Evaluation of antimicrobial property

21/10-

③ Cold cream & Vanishing cream -

* Creams -

· Creams are viscous semi-solid emulsions which are meant for external use. -

* Types of creams -

i) Aqueous creams - eg - Vanishing creams
ii) Oily creams - eg - Cold creams -

* Cold creams -	V/s	* Vanishing creams -
· These are w/o emulsion		· These are o/w emulsion -
· Applied on skin to provide smoothness & remove makeup		· Provide emollient & protective action to the skin against ev. -
		· To improve adhesion -
		· Also known as "Day creams" -
		· They are applied in the day times. -

* Formulation of creams - [Cold creams] -

· Ingredients -	Example -
i) Emulsifying agent & stabilizer	=> White beeswax -
ii) Lubricating agent	=> Liquid paraffin -
iii) Preservative	=> methyl paraben -

iv) Alkaline Subs which react with emulsifing agent to form a soap ⇒ Borax-
v) Solvent ⇒ Distill water-
vi) Aromatic agents ⇒ Perfume-

* Vanishing cream-

Ingredients	Examples-
i) Emulsifying agents & Stabilizer	⇒ Stearic acid-
ii) Humectants	⇒ Glycerin & Sorbitol
iii) Alkalies	⇒ Potassium hydroxide
iv) Solvent	⇒ Distill water
v) Aromatic agents	⇒ Perfume

* Preparation of creams-

* Cold creams-

- Beaker-1st
- Beeswax is melted at 70°c & add liquid paraffin-
- Beaker-2nd-
- water is heated at 70°C & borax dissolved-
- Beaker-2nd is added slowly to the mixture (beaker-1st) along with Stirring-
- Finally Perfume is add & formulation-

* Vanishing creams-

- Beaker-1st-
* Stearic acid melted at 75°c
- Beaker-2nd-
* KOH dissolved in water & glycerine is add & heated at 75°c (aqeous phase)-
* Slowly beaker-2nd is added to beaker-1st
* Finally perfume is add & formulation-

* Evaluation of creams-

i) In vitro method-
ii) In vivo method-

(4) Tooth paste-

- Denti-frices such as toothpastes-
- The cleaning the surface of the teeth by removing the food debris & plaque- (residue)

* formulation of toothpaste-

- Toothpastes are the most popular form of dentifrices.-

· Ingredient-	· Example-
· Polishing agents (Abrasive agents)-	⇒ PPt $CaCo_3$, phosphate of Ca^{2+}, Dental graded Silica-
· Foaming agents (Surfactants)-	⇒ Sod. lauryl sulphate, Sod. lauryl Sarosinate-
· Humectants	⇒ Sorbitol-70, Glycerin-
· Binding agents	⇒ Cellulose ethers, Gum-
· Sweeteing agents	⇒ Sodium Saccharin, Chloroform
· Flavouring agents	⇒ Cinnamon bark, Spearmint Oil etc-

* Preparation of toothpaste -

· Two methods -

i) Dry gum method -
ii) Wet gum method -

* Evaluation of toothpaste -

i) Determination of particle size -
ii) Test for abrasive character -
iii) Test for cleansing property -
iv) Determination of pH of the product -
v) Determination of foaming character -
vi) Limit test for heavy metals -

(5.) Hair dyes

· These are agents that responsible for variety of hair colour. -

* Only two variety of hair colour -
i) Pheo-melanins ⇒ Red & yellow -
ii) Eu-melanins ⇒ Dark brown & black -

** Hair dyes are the cosmetic preparation which are used by men & women change the natural hair colour -

* Hair dyes ⇒ Combination of pheomelanins & eumelanins -

* formulation of hair dyes -

· Ingredients -	· Examples
i) Formulation bases -	⇒ Amino dyes, ~~Ethyl~~
ii) Alkalizing agents -	⇒ Ammonia, mono-ethanolamine.
iii) Dyes components -	⇒ Pheomelanins & eumelanins -
iv) Oxidizing agents -	⇒ P. phenylene diamine -
v) Antioxidents -	⇒ Sodium sulfite
vi) Solvents -	⇒ Polar, Non-polar -
vii) Surfactants -	⇒ Alkanol-amide, Aniomic -

* Preparation of hair dyes -

· Prepare the mixture of surfactant + added dye
⇓
· Buffer & Colour compd. are dissolve in water
⇓
· ~~Aqueous~~ ~~Aqeus~~ Aqueous solution + dye with stirring
⇓
· Adjusted the viscosity of dye ⇒ formulation of dye.

* Evaluation of hair dyes -

i) The sensitization test -
ii) The toxic effect test -

01/11-

(6) Sun-Screens-

· Also known as "Sun-block, Sun-Cream, Suntan lotion-

* It is lotion, spray, gel foam & topical product that absorbs/reflects of the ultraviolet radiation

* It is help to protect against Sun-burn.-

* Formulation of Sunscreens-

· Ingredients	· Examples
· Emulsifying agents (Surfactants)	=> methyl salicylate-
· Humectants	=> Glycerin-
· Alkalin	=> Borax-
· Solvent	=> Alcohol, water-
· Aromatic agents	=> Perfume -

* Preparation of Sun Screens-

· Heat the water & dissolve water base compds with stir
⇓
· Other compounds mix with oil phase & mix
⇓ filter

formulation

(B) # Pharmaceutical aerosols #

01/11-

(a) * P'cal aerosols-

· The packing of therapeutic active ingredients in a pressurized system.-

* Aerosols => Pressurized package
=> Pressurized dosage form.

* Aerosols are depends on the "power of compressed" or liquefied gas to expel the contents from containers.-

(b) * Advantage-

· Easily withdrawn of drug-
· Easy & convenient to apply-
· Faster onset of action-
· Avoid the 1st pass metabolism-
· Provides efficacy of a drug-
· Irritation can be reduced-

(c) * Dis-advantage-

· Allergic in some cases-
· Costly-
· Some formulation is difficult-
· Explosive-
· Difficult disposal of empty aerosol containers
⇓ [Controll/arrangement]

(d) * Components of aerosols-Package-

i. Propellant-
ii. Container-

iii) Valve & actuator-
iv) Product concentrate-

i) Pro-pellant-
· It is responsible for developing the power pressure with in the container-
· It is also expel (repulse) the product when the valve is opened-

Types
(a) * For oral & inhalation- eg.- Fluorinated hydrocarb
(b) * Topical preparation- eg. Propane, Butane-
(c) * Compound gases - eg- N_2, CO_2 & NO -

* Physio-chemical properties of pro-pellants-
i) Vapor pressure-
ii) Boiling points-
iii) Liquid density-

ii) Containers-
· They must be stand at pressure as high as 140-180 Psig at 130°f -
(per square inch gauge)
a) metals containers-
b) Glass containers-

a) metals containers-

1) Tin-plated steel → Side-seam (three pieces)
→ Two-pieces (Drawn)-
→ Tin free steel-
2) Aluminium → Two-pieces-
→ one-pieces (Drawn/Extruded)-
3) Stainless steel-

b) Glass containers-
1) Uncoated glass-
2) Plastic coated glass-

iii) Valves-
· To give proper amount of medication-
* The present day aerosol valve is multifunctional-
* It is capable of being easily opened & closed.-

* Types of valves-

a) Continuous spray valve-
b) High speed production technique-
c) metering valves-

* Valve components.
a) ferrual (mount cap)-
b) Valve body (Housing)-
- Stem, Gasket, Spring & Dip tube-

iv) Actuator-
· To ensure that aerosol product is delivered-

* Types of actuator-

a) Spray actuator-
b) Foam actuator-
c) Solid Steam actuator-
d) Special actuator-

(e) * Types of aerosol Systems-

a) Solution System-
b) water based system-
c) Suspension (dispersion) Systems-
d) Foam Systems- i) Aqueous Stable foams-
ii) Non-aqueous Stable foams-
iii) Quick-breaking foams-
iv) Thermal foams-
e) Intra-nasal aerosols-

(f) * formulation & manufacture of aerosols-

* formulation of p'cal aerosols- Contains two essential components

a) Product concentrate-
b) Propellant-

a) Product concentrate-
· mixture of active ingredients & other such as solvents, anti-oxidants & surfactants-

b) Pro-pellant-
· may be single/blends of various propellants
· To give the desired vapor pressure, solubility & particle size-

* Parameters consideration-
· Physical, chemical & p'ceutical properties of active ingredients-
· Site of application-

* manufacturing of p'cal aerosols-
· Apparatus-
(g) i) Pressure filling apparatus-
ii) Cold filling apparatus-
iii) Compressed gas filling apparatus-

(h) * Quality control & stability studies-
i) Propellants-
ii) Valves, actuator & dip tubes-

iii) Testing proeedure - * Propellant -
iv) Valve acceptance - * Valve & actuator -
v) Containers - * Container -
vi) weight checking - * Leak testing -
vii) Leak testing - * weight testing -
viii) Spray testing -

* Evaluation of p'cal aerosols -

1. Flammability & combustibility -
2. Physio-chemical characteristics -
3. Performance -
4. Biologic characteristics -
5. Therapeutic activity -

1. Flammability & combustibility -

i) Flash point -
ii) Flame extension, including flashback -

2. Physio-chemical characteristics -

i) Vapor pressure -
ii) Density -
iii) moisture content -
iv) Identification of propellant -
v) Concentrate - propellant ratio -

3. Performance -

i) Aerosol valve discharge rate
ii) Spray pattern -
iii) Dosage with metered valves -
iv) Net contents → weight method -
v) Foam stability → visual evaluation
vi) Particle size determination → Cascade impactor
→ Light scatter decay method -
vii) Leakage -

* Flash point -
· Determined by using standard "Tag open cup" apparatus -

* Flame projection -
· Indicates the effect of an aerosol -

* Vapor pressure -
· Determined by "Pressure gauge" -

* Density -
· Determined by "Hydrometer or pychometer" -

* moisture content
· method used - "karl fischer method
· G.C. has also used.

* Identification of propellants -
· G.C. -
· I.R. - spectro~~scop~~ photom

(2) # Packaging materials science # 01/11-

(a) * P'cal packaging-

It is the science, art & technology of enclosing products for distribution, storage, sale & use.-

* Provide stability for a product during storage & transportation.-

* Functions of packaging-

i) Product protection-
ii) Product identification-
iii) Facilitating the use of product-
iv) Product promotion-
v) marketing-

* Selection of the packaging materials-

a) On the facilities available-
b) On the ultimate use of product-
c) On the physical form of the product-
d) On the route of administration-
e) On the stability of the materials-
f) On the cost of the product-
g) On the contents-

(b) * Types of packaging-

i. Primary packaging-
ii) Secondary packaging-

iii) Tertiary packaging -
iv) Unit-dose packaging -
v) Devices packaging -

i) Primary packaging -
- First envelops the product & holds -
- It is direct contact with the contents -

Example - Ampoules, Vials, containers, Dosing droppers, Closures (plastic, metal), Syringes, Strip packaging, Blister packaging -

ii) Secondary packaging -
- Outside the primary packaging. -

Example - Paper & boards, Cartons, Corrugated fibers, Box manufacture. -

iii) Tertiary packaging -
- Bulk handling, warehouse storage & transport shipping. -

* Two types of special packaging -

iv) Unit-dose packaging -
- Reducing medication errors
- Very useful in improving compliance with treatment -

v) Device packaging -
- Packaging with the aid of an administration device

Example - Syringes, droppers, transdermal delivery systems, pumps & aerosol sprays -

(2)* materials used for packaging of p'cal products -

1. Glass container -
2. metals container -
3. Rubber container - (Elastomers) -
4. Plastic container -
5. Fibrous material container -
6. Films, foils & laminates container

(1) Glass container -

- Widely used as a drug packaging material. -
- Si, Al, Na, K, Ca, Mg, Zn & Ba are generally used into preparation of glass -

* Types of glass -
i) Type-I - Neutral or Boro-silicate glass -
ii) Type-II - Treated soda lime glass -
iii) Type-III - Soda lime glass -
iv) Type-NP - General purpose soda lime glass -
v) Coloured glass -

* Example of glass container -
  - Ampoule, Vial, Bottles & Jars, Dropper & Aerosol Container.

* Test for glass container -
  - As I.P. & U.S.P. -
  i) Surface hydrolytic resistance -
  ii) Hydrolytic resistance of powdered glass.

(2) metals container

- Metal containers are used only for medicinal products for non-parenteral administration.
* It is the ideal packaging material for pressurized containers.-

* Types of metals container -

i) Aluminium -
ii) Tin -
iii) Lead -
iv) Linings.

* Examples of metal container -
  - Tubes, packs made from foil, blisters, Cans, aerosol & gas cylinder

(3) Rubbers (Elastomer) Containers -

- Excellent material for forming seals, used to form closures such as bungs for vials -

* Types of rubbers containers -

i) Natural rubbers containers -
ii) Synthetic rubbers Containers -

(4) Plastic containers -

* A wide range of solid composite materials

* Types of plastic containers -

i) Thermo-plastic type containers -
ii) Thermo setting type containers -

* Example of plastic containers -

- Plastic bottles made from PP, HDPE & PS -
- Plastic pouches —"— HDPE -
- Bottle made from PET -
- Spray made from PP -

* Test for plastic containers -
  i) Leak test -
  ii) Water permeability test -

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(5) Fibrous materials Containers-

· These are important part of p'cal packaging.-

* Include- Papers, Labels, Cartons, Bags, Outercases

(6) Films, foils & laminates-

· Applicable to tablets, Capsules & pills etc-

(3) * Factors influencing choice of containers-

a) Size & shape of material (product)-
b) Physical & chemical characteristics-
c) Types of formulation-
d) Route of administration of product-
e) Category of patient (Baby, child, adultsetc)-

(4) * Legal & official requirements for containers-

· They must be FDA approved-
· They must protect the preparation from environmental conditions-
· They must not be reactive with product
· They must be non-toxic-

01/11-

· They must not impart to the product tastes or odors-
· They must meet applicable tamper-resistance requirements-
· They must not be cause of product degradation

* Stability aspects of packaging materials-

· The developmental stage are done to provide a database-
· The help in selection of container closure systems-

* Packaging material include-

· Blister paks-
· Aluminium strip-
· Alu-Alu paks-
· HDPE- bottles-

· The storage condition to be selected
· The storage condition have been given by ICH & WHO.-
· Help to determine the adsorption of product components in to the container-closure.-

(7) * Quality control tests-

· Determination of quality, integrity & compatibility of packaging materials-

* Depends on type of p'cal materials used-
* Regulatory agencies like- WHO, GMP, USFDA & ICH guidelines-

(1) Evaluation of glass container-

i) Crushed-glass test => Official in USP-
ii) Whole-container test => official in European, British & international pharmacopoeias

(2) Evaluation of plastic container-

· Parenteral & non-parenteral preparations-

i) Leakage test-
ii) Clarity of aqueous extract-
iii) Transparency test-
iv) water vapour permeability test-

(3) Common physio-chemical test-

a) Appearance-
b) Light absorption-
c) pH-
d) Non-volatile matter-
e) Residue on ignition-
f) Heavy metals-
g) Buffering capacity-
h) Oxidisable substances-

(4) Common biological test-

i) Implantation test-
ii) Systemic injection test-
iii) Intra-cutaneous test-

* Pyrogens & endotoxin testing -

* Pyrogenic substances
  · Produced by gram (+) bacteria, mycobacteria, fungi & viruses -

* Pyrogens -
  · Produced by gram (-) bacteria & that is the endotoxins -

* Endotoxins ⇒ Found in the outer membrane of gram (-) bacteria -
* membrane → phospholipids called Lipo-polysaccharides
* The release of LPS from bacteria after death & lysis of the cell. -

(A) Introduction -

· Check the presence or absence of pyrogen in all aqueous parenteral preparation.

* Pyrogens are the metabolic product of micro-organisms.
* Pyrogens are produced by all micro-organisms.

** But - Gram ⊖ve bacteria produce most potent pyrogenic substances.
* Poly-saccharides & thermo-stable -
* Soluble in water
* Pass through bacteria proof filters -
* Unaffected by bactericide.

(B) Principle -

· The measurements of the rise in body temperature of rabbit -

(C) Materials required for the test -

i) Temperature recording device -
ii) Glass wares -
iii) Syringes & needles - } ⇒ Sterile -
iv) Retaining boxes for rabbits -
v) 3 - healthy adult rabbits - (weight NLT 1.5kg each) -

(D) Method -

· Test is carried out in an air condition room -

· Dissolve the substances & prepare saline solution pyrogen free -
· Warm the saline solution approximately 38.5°c -
· Volume of injection is NLT 0.5ml/kg & NMT 10ml/kg of body weight -
· Temp. device inserted into the rectum of the rabbit for recording the body temp. -
·
⇓
Initial temp. of rabbit -

* Solution injected slowly through ear vein volume 0.5 → 10ml/kg -
⇓
Record the temp. of each rabbit interval of 30 minutes → for 3 hours -

* Difference b/w initial temp. & maximum temp -

* When - Difference is negative ⇒ Result
· Zero response -

(E) Inter-pretation of result -

· 3 rabbit NMT 1.4°c -
· Individual rabbit LT 0.6°c (less than)
⇓
Test pass

* If the response of any rabbit is 0.6°C / more
• Sum of the responses 3-rabbits NMT 1.4°C -

⇓

• Continue the test using 5 other rabbit (3+5=8 rab)

• NMT 3 of 8 rabbits show individual responses 0.6°C/more
* Sum 8-rabbits NMT 3.7°C

⇓

Test pass